

REMARKS

Claims 4, 8, 12 and 14-82 have been canceled, and claims 1-3, 5, 9-11 and 13 have been amended to remove non-elected subject matter and to correct misspellings and grammatical mistakes. Upon entry of the foregoing amendments, claims 1-3, 5-7, 9-11 and 13 would be pending.

Applicants respectfully request reconsideration of this application in view of the foregoing amendments and in view of the following reasons.

35 U.S.C. 112, Second Paragraph

Claims 1, 2, 5, 6, 10 and 13 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In support of this rejection, the Office action states:

Claim 1 is ambiguous. It is very confusing on pages 121-123 with an enormous proviso conditions. It is unclear as to what is in and what is out i.e. whether all the provisos are operating simultaneously or one at a time etc. It is recommended that applicants limit the claim to the elected invention and claim *what is* applicants' invention instead of what is *not* applicants' invention.

Claim [sic] 2 and 10 are self-conflicting because claim 2 has the scope that "R₂ is carbocycle...containing CH₂..." which will not include phenyl yet on page 125, the R₂ moiety was either phenyl or phenyl tautomer.

Claims 5 and 13 are improper under modern claim practice. Please note that claims must under modern claim practice stand alone to define invention and incorporation into claims by express reference to specification is not permitted. See Ex parte Fressola 27 USPQ2d 1608. There is not reason why the names of the compound cannot be clearly named in claims. It is recommended that those compounds reading on the election be explicitly claimed by its name or structural formula.

It is unclear "what" is the structure of claim 6. If this is compound 43 on page 62, the nomenclature does not read on this compound. Clarification is requested.

The foregoing amendments obviate the rejection to claim 1. By canceling the non-elected subject matter, the foregoing amendments significantly reduce the number of provisos in claim 1. Furthermore, the "[t]he current view of the courts is that there is nothing inherently ambiguous or uncertain about a negative limitation. So long as the boundaries of the patent protection sought are set forth definitely, albeit negatively, the claim complies with the requirements of 35 U.S.C. 112, second paragraph." M.P.E.P. § 2173.05. The phrase "further provided" signifies that the provisos act simultaneously. Since the negative limitations are clearly defined, they do not render claim 1 indefinite.

Applicants respectfully traverse the rejection of claims 2 and 10. The definition of the R^2 moiety appears on page 125 as part of claim 3. Since claim 3 is dependent upon only claim 1, it does not incorporate the limitations of either claim 2 or 10. Thus, regardless of whether their respective definitions of R^2 actually conflict, claim 3 cannot render either claim 2 or 10 indefinite.

Applicants respectfully traverse the rejection of claims 5 and 13. Incorporation by reference to a table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993)(citations omitted). With over one hundred compounds in Tables I, II and III, it would be impractical to name every compound and it would be more concise to incorporate by reference.

Regarding claim 6, applicants confirm that the claimed compound is compound 143 on page 62.

35 U.S.C. 102(b)

Claims 1 and 2 have been rejected under 35 U.S.C. 102(b) as being anticipated by Bycroft et al. Claims 8 and 9 have also been rejected under 35 U.S.C. 102(b) as being anticipated by Gold et al., Baubaum et al. and Hamilton et al. (US 6,291,510).

Applicants respectfully traverse the rejections of claims 1, 2, 8 and 9. Claim 1 excludes Bycroft et al.'s compounds with the limitation: "further provided that when X is O, D is a bond, and R² is cyano, then R¹ is not methyl." Since claim 2 is dependent on claim 1, it also does not read on Bycroft et al.

The foregoing amendments obviate the rejection of claim 8. Regarding the rejection of claim 9, neither Burbaum et al. nor Gold et al. discloses a compound with applicants' R¹ moiety. Hamilton et al. is not prior art under 35 U.S.C. 102(b) because it was not patented more than one year before the effective filing date of this application.

35 U.S.C. 102(f)

Claims 1-3, 5, 8-11 and 13 have been rejected under 35 U.S.C. 102(f) as being anticipated by WO 99/14998.

Applicants respectfully traverse this rejection. WO 99/14998 claims priority to U.S. Provisional Application No. 60/059,905 filed on September 24, 1997, U.S. Provisional Application No. 60/059,963 filed on September 25, 1997 and U.S. Application No. 09/159,105 filed on September 23, 1998. Neither one of these provisional applications provides support for the subject matter relied upon by the

Office for this rejection. Thus, September 23, 1998 is the earliest priority date to which the relevant subject matter of WO 99/14998 may be entitled to claim.

This application is a divisional of U.S. Application No. 09/453,571 filed on December 2, 1999 (now US 6,331,537), which in turn is a continuation-in-part of U.S. Application No. 09/204,237 filed on December 3, 1998 (abandoned), which in turn claims the benefit of U.S. Provisional Application No. 60/087,788 filed on June 3, 1998 and U.S. Provisional Application No. 60/101,077 filed on September 18, 1998. These provisional applications provide support for the claimed subject matter that the Office contends is anticipated by WO 99/14998. Since the filing dates of these provisional applications precede WO 99/14998's priority date of September 23, 1998, WO 99/14998 is not prior art under 35 U.S.C. 102(f).

35 U.S.C. 102(e), (f) or (g)

Claims 1, 2 and 6-10 are rejected under 35 U.S.C. 102(e), (f) or (g) as being anticipated by Brumby et al. or Kato et al. supplemented by Andersen et al.

Applicants respectfully traverse this rejection. Prior U.S. Provisional Applications Nos. 60/087,788 and 60/101,077 provide support for the claimed subject matter that the Office contends is anticipated by Brumby et al. or Kato et al. Brumby et al.'s and Kato et al.'s earliest priority dates are March 24, 1999 and August 12, 1999, respectively. Since the filing dates of U.S. Provisional Applications Nos. 60/087,788 and 60/101,077 precede Brumby et al.'s and Kato et al.'s priority dates, neither Brumby et al. nor Kato et al. is prior art under 35 U.S.C. 102(e), (f) or (g), irrespective of the validity of their claims to priority.

35 U.S.C. 103(a)

Claims 1-3 and 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,859,031, US 5,945,441, US 6,177,455 and US 6,291,510 in view of Silverman or Bungaard further in view of US 5,801,187 and US 6,218,544.

The primary references, US 5,859,031, US 5,945,441, US 6,177,455 and US 6,291,510, may qualify as prior art only under one or more subsections (e), (f) and (g) of 35 U.S.C. 102 because they were patented after the effective filing date of this application. Under 35 U.S.C. 103(c), subject matter which qualifies as prior art only under one or more of subsections (e), (f) and (g) of 35 U.S.C. 102 shall not preclude patentability where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation to assignment to the same person. Since the subject matter of the primary references and the claimed invention were owned by or subject to an obligation to assignment to GPI NIL Holdings, Inc. at the time the claimed invention was made, none of the primary references may render the claimed invention unpatentable under 35 U.S.C. 103(a).

Obviousness-type Double Patenting

Claims 1-3 and 8-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4 and 18 of US 5,859,031 and claim 4 of US 6,291,510 in view of Silverman or Bungaard further in view of claims 1-8 of Li et al. US 5,801,187 and claim 1 of Li et al. US 6,218,544. In support of this rejection, the Office contends:

Hamilton '031...[and] '510 disclosed all the elements of the claims **except** the compounds are in form of an ester of the instant carboxylic acid or carboxylic acid isostere. Bungaard taught that ester is a "prodrug" of free carboxylic acid compounds since naturally, under physiological conditions,

the ester will be hydrolyzed to acid by esterases which can be found in the blood, liver and other organs or tissues (see Bungaard p. 3-4 para bridging) while Silverman taught the same concept further taught the same approach can be extend [sic] to sulfate or phosphate esters (see p. 356) and the modification of the ester moiety to increase the hydrolyzation rate (see p. 357).

Applicants respectfully traverse this rejection.

Determination of obviousness-type double patenting essentially involves the determination of obviousness under 35 U.S.C. 103, except that the first patent is not applicable as prior art. *In re Longi*, 759 F.2d 887, 892 n.4, 225 U.S.P.Q. 645, 648 n.4 (Fed. Cir. 1985). To establish a *prima facie* case of obviousness under 35 U.S.C. 103, the Office must show that: (1) the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated one of ordinary skill in the art to modify a reference (*In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988)); and (2) the proposed modification of the prior art must have had a reasonable expectation of success (*Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991)).

Nothing in the art suggests whether or not the esters of US 5,859,031 and US 6,291,510 are prodrugs. "Some prodrugs are not designed as such; biotransformations are fortuitous, and it is discovered after isolation and testing of the metabolites that activation of the drug had occurred." Silverman, p. 354. In view of the lack of evidence to date that the esters of US 5,859,031 and US 6,291,510 are prodrugs, one of ordinary skill in the art would have had no reason to expect at the time of the invention that the esters of US 5,859,031 and US 6,291,510 would undergo hydrolysis *in vivo*.

Even if one of ordinary skill in the art could have recognized the possibility of hydrolysis, that person could not reasonably have expected that the hydrolyzed esters (or carboxylic acids) would be active. Both Bungaard and Silverman

acknowledge that some esters are ineffective as prodrugs. "Sometimes, simple aliphatic or aromatic esters may not be sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion." Bungaard, p. 4. "[I]n some cases the esters are not very good substrates for the endogenous esterases, sulfatases, or phosphatases, and they may not be hydrolyzed at a rapid enough rate." Silverman, p. 356.

The esters of US 5,859,031 and US 6,291,510 have at least six positions for substitution, with the actual number potentially much higher depending upon the moieties selected at the R₁, X, Y and Z variable groups. Without knowing whether the esters are effective prodrugs, one of ordinary skill in the art would not have been motivated to modify the esters to arrive at applicants' claimed carboxylic acids.

Corrected Drawings

Corrected drawings are filed concurrently with this communication.

CONCLUSION

Applicants believe that this application is now in condition for allowance. Favorable reconsideration of this application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of this application.

Respectfully submitted,

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